Remarks

Restriction Requirement

Claims 6 and 9-13 were cancelled without traverse in view of the revised restriction requirement.

Obviousness-type double patenting

Claims 1-5, 7 and 8 were rejected under the doctrine of obviousness type double patenting over claims 1-3 of U.S. Patent No. 5,202,253 to Esmon, et al. This rejection is respectfully traversed if applied to the amended claims.

The limitations of claim 4 and 16 have been incorporated into claims 1 and 14, respectively. Claims 4 and 16 have been cancelled.

The standard for obviousness-type double patenting is whether the **claims of the present application, alone and without reference to the specification**, are obvious from the **claims, without reference to the specification**, of the cited patent. All of the claims define an antibody encoded at least in part by specific nucleotide sequences. "Inherency" has nothing to do with the issue at hand. Unless the encoding sequence is absolutely identical, and the antibody is expressed in the hybridoma deposited with the ATCC which is the subject of U.S. Patent No. 5,202,253, which is excluded from claim 1 as amended, the antibody is not the same. Support for the amendment is found for example at page 8, which describes the deposited antibody in the last paragraph, and describes the claimed antibodies as derived therefrom above it. In the absence of the nucleotide sequence, one could not make the

claimed antibody. It was established by the Court of Appeals in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995) that merely having the protein, or even some amino acid sequence (which is not described in the claims of the issued patent) would not be sufficient. The examiner has cited no art that discloses or makes obvious the amino acid sequence encoded by the recited nucleic acid. Accordingly, the claims cannot be obvious over the claims to the HPC-4 antibody as deposited with the ATCC and claimed in the '253 patent.

Claims 14-19 were rejected under the doctrine of obviousness-type double patenting over U.S. Patent No. 5,202,253 to Esmon, et al., in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). This rejection is also traversed.

The Examiner's attention is again drawn to in re Deul, which specifically rejects this argument, on the basis that a "plan" is not enough to make obvious a nucleotide sequence. Even though the claimed subject matter is an antibody, the antibody **cannot be made except by expression of the nucleotide sequence**; accordingly, the antibody cannot be obvious from the naturally occuring antibody.

Claim 6 was also rejected under the doctrine of obviousness type double patenting but this claim was already withdrawn from consideration by the Examiner.

Rejections under 35 U.S.C. §102(b)

Claims 1, 2, 4, 5, 7 and 8 were rejected under 35 U.S.C. §102(b) and (e) as disclosed by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 to Esmon, et al. or

'Angelo, et al., J. Clin. Invest. 77, 416 (1986) or Stearns, et al., J. Biol. Chem. 263, 826-832 (1988). These rejections are respectfully traversed if applied to the amended claims.

The claims have been amended to exclude the natural antibody disclosed in the '253 and '638 patents.

This amendment also excludes the antibody of Stearns, et al. and D'Angelo. However, it should be noted by the Examiner that both of these publications were overcome as prior art against the '253 and '638 patents as to the HPC-4 antibody on the basis that they were non-enabling and a number of experts in the field of anti-protein C antibodies testimony that they had tried for years unsuccessfully to obtain a similar anti-protein C and calcium binding antibody.

Rejections under 35 U.S.C. §103

Claims 1-8 and 14-19 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 to Esmon, et al. or 'Angelo, et al., J. Clin. Invest. 77, 416 (1986) or Stearns, et al., J. Biol. Chem. 263, 826-832 (1988) in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). These rejections are respectfully traversed.

As discussed above, HPC-4 as it was deposited with the ATCC has been excluded from the claims. As evidenced by the testimony in the '253 case, numerous experts testified that even with undue experimentation they were unable to make by standard techniques monoclonal antibodies havin the unique specificity of HPC-4: binding with one part of the antibody a peptide epitope and binding with another part of the antibody calcium. Until one

had actually cloned the nucleotide sequence encoding HPC-4 and expressed it, it was not possible to predict that the isolated nucleotide sequence encoded HPC-4, much less whether it would be expressed in functional form. Humanized antibodies having the same specificity have now been made using standard techniques, based on the disclosed nucleotide sequence, by Genentech. In the absence of the nucleotide sequence, one cannot modify and genetically engineer the antibody to include humanized sequence, nor as claimed in the new claims 20 and 21, make a fusion protein (as described in the application at page 8, lines 20-25, and page 21, lines 13-32). These claims do not exclude HPC-4 explicitly, since HPC-4 as deposited with the ATCC is not a fusion protein.

Applicants agree that one skilled in the art would have been motivated to do what applicants have done. However, there is a huge difference between being motivated "to try" to do something and "being obvious". It was simply not predictable that one could clone the genes and express a recombinant antibody, much less with this unique specificity. No art has been cited showing it was routine to clone antibodies. Morrison is directed at transfection; not cloning. Queen is evidence that it was possible to make humanized antibodies; not that it was routine to clone them, especially antibodies of the claimed unique, bi-functional binding specificity.

Rejections under 35 U.S.C. §112

Claims 2, 4, 15 and 16 were rejected under 35 U.S.C. §112 as non-enabled unless limited to the sequences of SEQ ID No. 10 and SEQ ID No. 12. Claims 1-8 and 14-19 were rejected under §112 as indefinite. These rejections are respectfully traversed if applied to the

amended claims. It is again noted that the Examiner withdrew claim 6 from consideration but seems to have examined the claim. Clarification would be appreciated.

First, it should be noted that all of the claims are limited to a defined binding specificity. Accordingly, if the antibody does not have this specificity, it is not within the scope of the claims.

Second, as discussed above, scientists at Genentech have made several humanized antibodies based on the disclosed sequences. This work is in press and will be publicly available to demonstrate that a variety of combinations of the claimed sequences can be used to make humanized antibodies. To the extent this relates to the indefiniteness rejection, the Examiner is requested to telephone the undersigned so that the rejection relating to CDRs can be understood.

The claims have been amended to clarify the binding specificity and to insert the term "composition" as applied to a pharmaceutical composition. "an" has been inserted into claims into claims 2 and 15.

The problem with claim 8 is not understood.

Claims 3, 8 and 16 have been amended in an attempt to respond to the examiner's rejections. Further guidance if the amendments do not overcome the rejections would be appreciated.

Allowance of all claims 1, 3-5, 7, 8, 14, 15, and 17-19 as amended, and new claims 20 and 21, would be appreciated. All claims as now pending are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

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Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Transmittal Letter, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: March 19, 1996

Claims as currently pending

1. (amended) A recombinant Ca^{2+} dependent monoclonal antibody immunoreactive with [an] a first epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with a second epitope consisting of calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, and wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate sequences thereof, and wherein the antibody is not the HPC-4 antibody deposited with the American Type Culture Collection as ATCC No. HB 9892.

2. (amended) The antibody of claim 1 comprising an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. (amended) The antibody of claim 1 containing human amino acid sequence other than the sequence defining the epitope binding specificity.

Please cancel claim 4.

5. (amended) [The] A composition comprising the antibody of claim 1 [further comprising] in combination with a pharmaceutically acceptable carrier for administration to a patient.

Please cancel claim 6.

7. The antibody of claim 1 having a detectable lable bound to the antibody.

8. (amended) The antibody of claim 1 immobilized to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

Please cancel claims 9-13.

14. (amended) A method of making a recombinant Ca^{2+} dependent monoclonal antibody immunoreactive with [an] a first epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with a second epitope consisting of calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, by expressing nucleotide sequence encoding the antibody, wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG

GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate sequences thereof, and is not HPC-4 antibody as deposited with the American Type Culture Collection as ATCC No. HB 9892.

15. (amended) The method of claim 14 wherein the antibody comprises an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

Please cancel claim 16.

17. (amended) The method of claim 14 further comprising inserting human sequence into the antibody in place of animal sequence other than the sequence defining the epitope binding specificity.

18. The method of claim 14 further comprising binding detectable lable to the antibody.

19. (amended) The method of claim 14 further comprising immobilizing the antibody to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

Please add the following new claims.

20. A recombinant HPC-4 antibody as deposited with the American Type Culture Collection as ATCC No. 9892 expressed as a fusion protein.

21. A method for making a recombinant HPC-4 antibody wherein a nucleotide sequence encoding HPC-4 antibody as deposited with the American Type Culture Collection as ATCC No. 9892 is ligated to a sequence encoding a different protein and expressed in an expression system as a fusion protein.